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Sepsis: A Review for the Neurohospitalist

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Abstract

Sepsis represents a major challenge in medicine. It begins as a systemic response to infection that can affect virtually any organ system, including the central and peripheral nervous systems. Akin to management of stroke, early recognition and treatment of sepsis are just as crucial to a successful outcome. Sepsis can precipitate myasthenic crisis and lead to encephalopathy and critical illness neuropathy. Stroke and traumatic brain injury can predispose a patient to develop sepsis, whereas Guillain-Barré syndrome is similarly not uncommon following infection. This review article will first describe the essential principles of sepsis recognition, pathophysiology, and management and will then briefly cover the neurologic aspects associated with sepsis. Vigilant awareness of the clinical features of sepsis and timeliness of intervention can help clinicians prevent progression of this disease to a multisystem organ failure, which can be difficult to reverse even after the original source of infection is under control.

Keywords

sepsis, septic shock, neurocritical care

> Except on a few occasions the patient appears to die from the body's response to infection rather than from the infection itself.
>
> William Osler, *The Evolution of Modern Medicine*, 1904.

Epidemiology

In 2009, septicemia was listed as the 11th leading cause of death in the United States.[1] More than 750 000 cases of sepsis are admitted every year to American hospitals, with more than half of these developing septic shock, ultimately resulting in 215 000 deaths.[2] Its incidence is thus comparable to the number of people developing the first heart attack (875 000) or stroke (700 000); its annual mortality also approximates that of acute myocardial infarction (221 000) and cerebrovascular accidents (273 000).[3]

A review of hospital discharge data from 1979 to 2000 revealed that while the total in-hospital mortality rate for sepsis appeared to be on the decline from 27.8% during the period from 1979 through 1984, to 17.9% during the period from 1995 through 2000, there was an annual increase in incidence of 8.7%.[4] A 2011 report by the Centers of Disease Control reviewing hospital discharge data indicated that hospitalizations with sepsis increased by 70% from 621 000 in 2000 to 1 141 000 in 2008.[5] Similarly, the number of hospitalizations for severe sepsis per 100 000 persons increased from 143 in 2000 to 343 in 2007, as the mean number of organ system failures increased from 1.6 to 1.9. However, while the mean length of hospital stay for severe sepsis in a more recent report[6] decreased from 17.3 to 14.9 days and the mortality rate decreased from 39% to 27%, more admissions ended with discharge to a long-term care facility in 2007 than in 2000 (35% vs 27%). Therefore, despite advances in therapy and given an increasingly aging population, overall mortality figures remained relatively stable. The annual inpatient costs of treating septicemia were estimated at $14.6 billion in 2008, and the costs of subsequent outpatient care are only expected to grow.[5]

Definitions and Diagnosis

The origin of the term sepsis can be traced to Homer poems over 2 700 years ago, where it was used as a derivative from the verb "sepo" meaning "I rot."[7] The term was then used by Hippocrates, Aristotle, Plutarch, and Galen, essentially without change in meaning.[7] Modern understanding of sepsis pathophysiology first became evident in Schottmüller's 1914 description of septicemia as a state of microbial invasion into the bloodstream causing signs of illness.[8]

In 1992, the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference arrived at the current definitions of sepsis as a continuum

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of increasing severity of presentations.[9] These definitions were revised in 2010.[10]

Systemic Inflammatory Response Syndrome

Systemic inflammatory response syndrome (SIRS) is diagnosed when a patient has 2 or more findings of body temperature above 38°C or below 36°C; heart rate above 90 per minute, respiratory rate of over 20 per minute, or a $Paco_2$ below 32 mm Hg; and a white blood cell (WBC) count over 12 000 cells/μL or below 4000 cells/μL or more than 10% bands.[9] The more recent revision to sepsis definitions removed the SIRS criteria, as it was felt that the criteria were too sensitive and nonspecific.[10]

Sepsis

Sepsis includes infection, documented or suspected, and some of the signs and symptoms of an inflammatory response (in adults)[10]:

- General variables: fever or hypothermia (core temperature >38.3°C or <36°C), heart rate >90 per minute, tachypnea, altered mental status, significant edema or positive fluid balance (>20 mL/kg over 24 hours), and unexplained hyperglycemia.
- Inflammatory variables: leukocytosis (WBC >12 000 cells/μL), leukopenia (WBC <4000 cells/μL), or >10% bands, increased C-reactive protein, and increased procalcitonin.
- Hemodynamic variables: arterial hypotension (systolic blood pressure <90 mm Hg, mean arterial pressure [MAP] <70), mixed venous oxygen saturation >70%, and cardiac index >3.5 L/min.
- Organ dysfunction variables: arterial hypoxemia, acute oliguria, creatinine increase >0.5 mL/dL, coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 seconds), ileus, thrombocytopenia (platelet count <100 000 cells/μL), and hyperbilirubinemia (>4mg/dL).
- Tissue perfusion variables: unexplained hyperlactatemia (>1 mmol/L), decreased capillary refill, or skin mottling.

Severe Sepsis

Severe sepsis is sepsis complicated by organ dysfunction.

Septic Shock

Septic shock is severe sepsis plus acute circulatory failure characterized by persistent arterial hypotension despite adequate volume administration, unexplained by causes other than sepsis.[10]

In general, most chronic disease states can predispose to sepsis: diabetes, chronic liver or kidney disease, malignancy, or use of immunosuppressive medications. Indwelling catheters or other devices put patients at an additional risk just like major surgery, trauma, or burns. More than one source of infection can be present and can be particularly challenging to identify in neutropenic or immunosuppressed individuals.

Pathophysiology

Sepsis begins with a source of infection anywhere within the body—skin, urinary tract, peritoneal cavity, lungs, and others. As the organism replicates, antigens are released by the body to elicit a systemic inflammatory response to aid in eliminating and limiting the invading pathogens. In addition, many elements of invading organisms can also induce systemic inflammation: endotoxins of the gram-negative bacteria, exotoxins of the gram-positive bacteria, lipoarabinomannan of mycobacteria, mannoproteins and β-glucan of fungi, to name a few.[11] As microbial components are identified by specific pattern recognition molecules (CD14 cells and Toll-like receptors), a complex process of cellular activation ensues, consisting of release of cytokines; activation of neutrophils, monocytes, and endothelial cells; neuroendocrine involvement; and activation of the complement, coagulation, and fibrinolytic systems.[8]

Tumor necrosis factor-α (TNF-α) and interleukins 1 and 6 (IL-1 and IL-6), secreted by monocytes and macrophages, initiate a multitude of subsequent inflammatory reactions.[8] Progressive endothelial dysfunction leads to increased microvascular permeability, and upregulation of platelet-activating factor results in platelet slugding.[12] Induction of tissue factor expression activates the extrinsic coagulation pathway leading to the formation of microvascular thrombi disturbing organ microcirculation and promoting the development of organ dysfunction.[13] Patients with sepsis frequently manifest disseminated intravascular coagulation with consumption of platelets and prolongation of clotting times. Overexpression of inducible nitric oxide synthase leads to increased levels of nitric oxide (NO) and production of reactive nitrogen species, as well as alteration in the microvascular homeostasis: in sepsis, NO is unequally distributed in the vascular system, accounting for the observed heterogeneity in tissue perfusion.[14] Nitric oxide diffuses to adjacent smooth muscle and activates cyclic guanosine cyclic monophosphate production ultimately leading to the profound loss of arterial vascular tone and venodilation seen in septic shock.[14]

To maintain homeostasis, the next phase in response to the systemic activity of proinflammatory cytokines is the compensatory anti-inflammatory response syndrome characterized by the release of cytokine inhibitors (IL-1 receptor antagonist) and anti-inflammatory cytokines (TGF-β, IL-4, IL-10, and IL-13).[15] In some patients, the compensatory reaction may be as excessive as the proinflammatory response, resulting in immunosuppression.[16] A recent postmortem examination of spleen and lung tissues of 40 patients who died in intensive care units (ICUs) with active severe sepsis showed increased expression of inhibitory receptors and ligands and expansion of suppressor cell populations in both organs.

Immunohistochemical staining demonstrated extensive depletion of splenic CD4, CD8, and HLA-DR cells and expression of ligands for inhibitory receptors on lung epithelial cells, which is consistent with immunosuppression.[17]

Ultimately, clinical manifestations and patient outcome depend on the balance between proinflammatory and anti-inflammatory components. Predominance of the inflammatory response may lead to cardiovascular compromise, shock, and organ dysfunction, while a predominance of anti-inflammatory mediators produces a state of immune paralysis associated with a propensity to develop infection.[16] Either may ultimately lead to death. Overall, the pathophysiology of sepsis is much more intricate but a more detailed description would be beyond the score of this review.

Management

Given the complexity of sepsis and high mortality rate, an international group of experts in the diagnosis and management of infection and sepsis established the first guidelines for physicians with the goal to improve outcomes in severe sepsis and septic shock.[18] A Surviving Sepsis Campaign was thus launched, and as more organizations joined and the understanding of sepsis increased, the guidelines were updated.[19] The guidelines include a statement saying that "the committee believes that currently, the greatest outcome improvement can be made through education and process change for those caring for severe sepsis patients in the non-ICU setting and across the spectrum of acute care."[19] Perhaps the most important aspect of sepsis interventions is implementing them early, which cannot be overemphasized.

A basic initial strategy to sepsis management consists of "SAVE": Suspicion, Act, Ventilation/oxygenation, Evaluate goals.[20] "Suspicion" entails recognition of the systemic inflammatory response as well as of sepsis manifesting in organ dysfunction and hypotension. "Act" stands for establishing and maintaining adequate perfusion and giving early antibiotics as well as pressors when necessary. Early mechanical "ventilation" with lung-protective settings is the third step. "Evaluation" of goals consists of assessment of lactic acid clearance, central venous oxygen saturation, hemoglobin levels, and MAP with initiation of inotropes when needed. We will discuss each of the steps in sepsis management below.

Initial Resuscitation

Early Antibiotics

The Surviving Sepsis Campaign recommends that intravenous antibiotic therapy be started as early as possible and within the first hour of recognition of septic shock and severe sepsis, with cultures obtained before initiation of antibiotics, provided this does not delay antibiotic administration.[19] However, this infrequently happens under real-life conditions. Kumar et al investigated the relationship between mortality and the duration of hypotension before the administration of antimicrobial therapy by examining medical records of 2731 adult patients with septic shock.[21] Survival rate was 82.7% if effective antimicrobials were administered within 30 minutes of the initial evidence of hypotension, and it decreased to 42% by the sixth hour. Overall, the adjusted odds ratio (OR) was 1.12 per hour delay, translating to a 12% decreased probability of survival per each hour of delay. Subgroup analysis demonstrated that the relationship between mortality and antibiotic delay persisted whether the infection was suspected or documented, the culture was positive or negative, the etiology was with gram-positive/-negative or fungal organisms, community acquired or nosocomial, and regardless of the source of infection or neutropenia. In that study, only 14.5% of all patients received antibiotics within the first hour of documented hypotension, and even 12 hours after the first episode of hypotension, 28.8% of patients had not received antimicrobial therapy.[21]

Reasons for the delay in administering antibiotics are numerous: failure to recognize infection in a timely way, failure to recognize that hypotension represents septic shock, failure to appreciate the risk of resistant organisms in certain scenarios (eg, immunosuppressed patient and antecedent antimicrobial use), waiting for blood sampling for cultures before giving antibiotics, requirement for 2 nurses to check for potential drug sensitivity before dosing of antimicrobials, transfer from emergency room before ordered antibiotics are given, failure to use "stat" orders, failure to recognize that administration of inappropriate antimicrobials is equivalent to absent antimicrobial therapy when responding to clinical failure (ie, should not delay appropriate antimicrobials because inappropriate drugs were recently given), no specified order (sequence) in multiple drug regimens so that the key drug (usually most expensive and most difficult to access) may be given last, administrative/logistic delays (nursing/pharmacy/ward clerk), and so on.[22]

Choice of antimicrobials is therefore crucial, as the administration of inappropriate therapy without activity for the given pathogen is equivalent to no therapy at all. In the review of 10 319 418 cases of sepsis between 1979 and 2000, authors remarked that the rate of sepsis due to fungal organisms increased by 207%, with gram-positive bacteria becoming the predominant pathogen after 1987.[4] Management of pseudomonas infection requires a high index of suspicion, including individuals with diabetes, with compromised immune system, on hemodialysis, or residing in a nursing home. In a study evaluating the impact of inappropriate therapy on pseudomonas bacteremia outcome, 39.6% of patients received inadequate empiric treatment resulting in higher mortality.[23] Another infection where appropriate therapy is often delayed is candidemia. In a study by Garey et al, mortality rates were 15% for patients who received appropriate therapy on day 1 compared with the 41% in those who received antifungal therapy by day 3 or later.[24]

Of note, antibiotic use 3 months prior to hospitalization is associated with increased likelihood of developing multidrug-resistant bacteria as shown by Seguin et al.[25] It is also

associated with decreased bacterial susceptibility and increased hospital mortality in patients with severe sepsis or septic shock from gram-negative bacteremia. In a recent study examining the outcomes of patients with recent antibiotic exposure compared to those without, patients with recent antibiotic use had significantly higher rates of resistance to antimicrobials and greater likelihood of inappropriate initial antimicrobial therapy and hospital mortality.[26] While important to always consider the issue of antibiotic resistance, this should not influence early administration of broad -spectrum antibacterial coverage in patients with sepsis. However, it does dictate the need for daily reassessment of antibiotic needs and deescalation as early as clinically justified.

Early Source Control

The Surviving Sepsis Campaign recommends that specific anatomic site of infection should be established as rapidly as possible and within the first 6 hours of presentation.[19] Essentially, source control consists of "all physical measures undertaken to eliminate a source of infection, to control ongoing contamination, and to restore premorbid anatomy and function."[27] It is guided by 4 principles: drainage, debridement plus device removal, decompression, and restoration of anatomy and function. When clinical examination does not reveal the source, computed tomography imaging would detect the majority of infection sources. Promptness of surgical intervention should be guided by the source: if rapidly progressive disease (necrotizing skin and soft tissue infections or gastrointestinal tract perforation) is present, those patients would need to be operated on within 1 to 2 hours after diagnosis, while someone with infected pancreatic necrosis would likely benefit from delaying the surgery until the infectious process has subsided.[27]

Early Goal-Directed Therapy

Early goal-directed resuscitation has become the cornerstone of sepsis management since the publication of the historic work by Rivers et al in 2001.[28] Authors randomized 263 patients to either 6 hours of standard (control) therapy (consisting of maintenance of central venous pressure [CVP] in the range of 8-12 mm Hg, MAP $\geq$65 mm Hg, and urine output $\geq$0.5 mL/kg per h) or early goal-directed therapy (standard therapy as above plus central venous—superior vena cava venous oxygen saturation [$ScvO_2$]—oxygen saturation $\geq$70%, arterial saturation $\geq$93%, and hematocrit $\geq$30%). Antibiotics were given as per the treating physician's discretion. Authors found that mortality in early goal-directed therapy group was 30.5% compared with 46.5% in the standard therapy group.[28] These findings stirred much debate in the critical care world and many publications followed including the work by Jones et al comparing lactate clearance to central venous oxygen saturation. The authors reported that the management guided by lactate clearance was comparable with the management guided by $ScvO_2$ with regard to mortality.[29] This could be particularly applicable in places with limited resources. Currently, the Surviving Sepsis Campaign recommends the following initial resuscitation measures: CVP 8-12 mm Hg (12-15 mm Hg if mechanically ventilated), MAP $\geq$65 mm Hg, urine output $\geq$0.5 mL/kg per h, $ScvO_2$ $\geq$70%, and if the target saturation is not achieved, fluid or transfuse packed red blood cells are given, if required, to hematocrit of $\geq$ 30% and/or dobutamine infusion up to 20 μg/kg per min.[19] It is important to emphasize that these steps were part of the multistep protocol that significantly reduced hospital mortality and, as such, has been widely accepted. However, there is insufficient evidence to support some of the steps individually. For example, even though red blood cell transfusion was thought to improve oxygen delivery, it was not shown to increase oxygen consumption.[19] A recent Transfusion Requirements in Critical Care trial demonstrated that target hemoglobin of 7 to 9 g/dL did not result in increased mortality compared with 10 to 12 g/dL.[30] Furthermore, transfusion of red blood cells and platelets is associated with increased incidence of secondary bacterial infections in patients with sepsis and pulmonary complications such as transfusion-related acute lung injury (ALI) and transfusion-associated circulatory overload.[31] Therefore, restrictive blood transfusion practices appear to be safe for the majority of critically ill, including neurocritically, ill patients. It is important to stress that there is no magic hemoglobin target for all patients, but this rather needs to be individualized by weighing all the risks and benefits of transfusion of blood products at the bedside. Similarly, liberal use of dobutamine is discouraged as it has arrhythmogenic potential and may increase an already elevated heart rate in patients with sepsis, which may further complicate the care of the patient. The key component of Early Goal Directed Therapy (EGDT) seems to be early adequate fluid resuscitation (starting in the emergency room); this alone would potentially have made a crucial impact and significant difference in patient outcomes.[32] One should therefore exercise caution before transfusing septic patients with hemoglobin less than 10g/dL, and dobutamine use should be avoided in the absence of myocardial dysfunction, particularly in the presence of significant tachycardia.

Early Initiation of Mechanical Ventilation

Septic shock increases the work of breathing, which can lead to hypoxemia and worsen acidosis, increasing the likelihood of developing ALI and/or acute respiratory distress syndrome (ARDS). Therefore, early initiation of mechanical ventilation may be beneficial. The Surviving Sepsis guidelines recommend targeting a tidal volume of 6 mL/kg of predicted body weight to avoid lung injury with a plateau pressure of less than 30 cm H_2O; if the plateau pressure remains elevated, further reduction in tidal volume to as low as 4 mg/kg may be warranted.[19] These recommendations are based on a landmark Respiratory Management in Acute Lung Injury/ARDS (ARMA) trial, which demonstrated a 9% decrease in mortality and in the number

of days on the ventilator, using a low tidal volume and plateau pressure setting.[33] Since $Paco_2$ is expected to rise above baseline with lung protective ventilation, permissive hypercapnia should be allowed in patients with ARDS, if necessary; setting positive end-expiratory pressure (PEEP) level >5 to avoid lung collapse at end expiration is also important.[19]

Hemodynamic Support and Adjunctive Therapy

Fluids

The Surviving Sepsis Campaign recommends fluid resuscitation with either colloids or crystalloids, as there is no evidence-based support for one type of fluid over another.[19] The Saline versus Albumin Fluid Evaluation study investigators randomized 6997 patients to either 4% albumin or saline and found no difference in outcomes at 28 days. However, in a subgroup analysis of patients with severe sepsis, there was a trend favoring albumin (relative risk [RR] = 0.87, $P = .06$).[34] Use of hydroxyethyl starch has been controversial, as many preparations are available; some studies documented increased risk of acute renal failure,[35] while others contradicted those findings.[36]

Pressors

In order to maintain adequate blood pressure to ensure organ perfusion in those refractory to fluid challenges, the Surviving Sepsis Campaign recommended using either norepinephrine or dopamine as a first-line agent to maintain an MAP $\geq$65 mm Hg.[19] However, in a subsequently published trial of 1679 patients randomized to norepinephrine versus dopamine, a subgroup analysis showed that dopamine was associated with an increased rate of death at 28 days among the 280 participants with cardiogenic shock.[37] A recent review of 6 trials comparing the 2 agents confirmed superiority of norepinephrine over dopamine on the 28-day mortality (pooled RR = 0.91) as well as significantly fewer arrhythmias in the norepinephrine group.[38] Epinephrine is recommended as a second agent in those refractory to norepinephrine.[19] Additional recommendations include use of vasopressin as a second agent in patients with less severe shock, as it may reduce norepinephrine requirements based on a subgroup analysis in Vasopressin and Septic Shock Trial (VASST), demonstrating a trend toward decreased mortality in those patients.[39] Post hoc analysis of VASST data for interaction of vasopressin infusion, corticosteroid treatment, and mortality revealed that low-dose vasopressin infusion plus corticosteroids significantly decreased the 28-day mortality compared with corticosteroids plus norepinephrine.[40] Interaction between vasopressin and steroids may be multifactorial and involves vasopressin-mediated adrenal corticotropic hormone (ACTH) secretion by corticotropic cells through V1b receptors[41] and restoration of vasopressin receptor sensitivity by corticosteroids.[42] In a recent retrospective study of 159 patients with severe septic shock, concomitant use of vasopressin and hydrocortisone was associated with a trend toward lower ICU and 28-day mortality, using the Cox proportional hazard model but not using other statistical analyses, possibly due to a lack of power.[43]

Corticosteroids

Despite decades of research, the role of steroids in the management of septic shock remains controversial. The Surviving Sepsis Campaign recommends that intravenous hydrocortisone (not dexamethasone) only be given to adult patients with septic shock after blood pressure is identified to be poorly responsive to fluid resuscitation and vasopressor therapy; they also recommend against ACTH stimulation test.[19] These recommendations are largely based on the results of a trial by Annane et al of 300 patients randomized within 8 hours to either hydrocortisone and fludrocortisone or placebos; in patients with relative adrenal insufficiency, there were fewer deaths among those receiving steroids (hazard ratio, 0.67).[44] However, subsequently, the multicenter Corticosteroid Therapy of Septic Shock study of 499 patients randomized within 72 hours failed to demonstrate a mortality difference regardless of corticotropin responsiveness.[45] Additional subgroup analysis of the 96 patients who received etomidate revealed that, although there were predictably more ACTH nonresponders in that group, etomidate use was associated with a higher mortality risk (OR = 1.7), and administration of hydrocortisone did not influence the outcomes.[46] Given such discordant results (which may be somewhat difficult to compare, given the differences in randomization times between the studies), recommendations of the Surviving Sepsis Campaign should be used with caution. Nonetheless, a recent report from the PROmoting Global Research Excellence in Severe Sepsis registry on global utilization of low-dose corticosteroids found that 14.2% of patients received the medication despite the absence of evidence of shock.[47] To better clarify the relationship between steroids and mortality, a recent review of 17 trials found that there was a lower mortality rate in the control compared with treated group (RR = 0.84), with steroids increasing the risk of hyperglycemia and hypernatremia.[48] Nonetheless, we may not have a final verdict regarding steroids just yet, as both Annane et al and CORTICUS investigators used total cortisol levels to assess adrenal function, whereas only free cortisol is biologically active, and its fraction could be higher than expected in sepsis due to a decrease in both corticosteroid-binding globulin and albumin. A recent investigation found that salivary cortisol, which is easy to measure, exhibited a high correlation with free serum cortisol in patients with septic shock and could thus be used as a surrogate.[49] This might help with a better understanding of the role of steroids in sepsis in the future.

Recombinant Human-Activated Protein C

In October 2011, the US Food and Drug Administration (FDA) issued a voluntary market withdrawal of recombinant

human-activated protein C due to its failure in showing a survival benefit.[50]

Glucose Control

Just like most other sepsis management issues, this topic has not been spared its share of controversy. More than a decade ago, a single-center study from Belgium demonstrated that intensive insulin therapy to maintain blood glucose at or below 110 mg/dL reduced mortality among critically ill patients in the surgical ICU.[51] Subsequently, 2 multicenter trials (NICE-SUGAR[52] and VISEP[53]) were stopped earlier than planned due to hypoglycemic and other adverse events in the intensive therapy groups. Stress hyperglycemia is not uncommon in critically ill patients and is a consequence of excessive hepatic glucose production and insulin resistance in response to cortisol, growth hormone, cytokines, and glucagon. A recent study investigated the effects of stress hyperglycemia in patients with sepsis and found that it was associated with reduced ICU mortality.[54] A possible explanation for that effect may be the impairment in oxygen delivery in a setting of hyperdynamic circulation, which might imply that glucose delivery could be impaired as well, thus requiring a higher glucose concentration gradient to deliver glucose from blood to cells. Current guidelines recommend using a protocol targeting glucose levels to the <150 mg/dL range[19] for the majority of hospitalized patients, including neurocritically ill.

Neurological Complications of Sepsis

Sepsis-Associated Encephalopathy

Altered mental status is present in up to 23% of patients with sepsis and can even precede the cardinal findings of sepsis particularly in older or immunosuppressed individuals. It is associated with a substantial increase in mortality of up to 49%, compared with 26% in those without neurologic symptoms.[55] Sepsis-associated encephalopathy (SAE) is distinct from delirium in that it can be one of its causes, but delirium is not the only clinical presentation of SAE.[55]

In fact, presentation of SAE is highly variable. In early stages, patients display impaired attention, concentration, confusion, and disorientation. Progression is characterized by paratonic rigidity and increasing depression in consciousness; in its last stage patients are comatose. Signs commonly seen with metabolic encephalopathy such as asterixis, tremor, and myoclonus are generally not seen in SAE. Also absent are cranial nerve abnormalities, and neurological findings are symmetrical.[56]

Even though SAE has been well documented in the literature, recognizing it in clinical practice can be challenging. Meningitis or brain abscess should be ruled out if applicable.[57] Causes of encephalopathy in a patient with sepsis are multiple, and it is important to exclude other potential contributing factors such as hepatic dysfunction, electrolyte and acid–base imbalances, hypoxemia, extremes of temperature, nutritional deficiencies, endocrine abnormalities and hypoglycemia, drug effects, alcohol withdrawal, to name a few.[55,57] Given such multifactorial, complex nature of encephalopathy, a physician should not cease his or her investigations once a single factor has been identified.[57]

Pathophysiology underlying SAE is not quite clear. Zampieri et al[55] provided a review of proposed mechanisms which consist of an inflammatory response-mediated direct cellular damage to the brain due to TNF-α induction, which leads to endothelial dysfunction and blood–brain barrier damage as well as the liberation of aquaporin 4 and brain edema. Also, mitochondrial dysfunction and reduction in oxidative phosphorylation can lead to cytochrome c malfunction and trigger apoptosis resulting in brain injury. Increase in large, neutral amino acids and decrease in branched-chain amino acids can lead to accumulation of false neurotransmitters and increase in intracellular calcium content both of which can contribute to encephalopathy. Additionally, altered cerebral perfusion can render brain function more susceptible to injury.[55]

Diagnostically, SAE is accompanied by abnormal electroencephalography (EEG) that can manifest excessive theta, predominant delta, triphasic waves, or burst suppression; however, none of the EEG findings are pathognomonic, and its usefulness in aiding SAE diagnosis also lies in exclusion of nonconvulsive status epilepticus.[55,57] Additional findings may include alteration of somatosensory-evoked potential latency or amplitude and elevated plasma levels of neuron-specific enolase and S100 β protein.[57] Brain imaging findings in patients with SAE may include white matter lesions (leukoencephalopathy) which are likely related to damage of the blood–brain barrier; posterior reversible encephalopathy has also been linked to sepsis, although it is generally a late finding.[55] No specific effective therapeutic strategies exist, and management consists of treatment of the underlying condition. Administration of branched chain amino acids has been tried to reverse the branched-chain/large amino acid ratio but no clear benefits have been demonstrated.[56] Dexmedetomidine has been associated with less delirium in patients with sepsis than continuous lorazepam and midazolam, possibly via reduction in apoptosis by binding to $\alpha 2$ receptors in addition to avoidance of well-known adverse effects of benzodiazepines.[55]

Long-term cognitive and psychological consequences of SAE are unknown. Although SAE is considered a reversible phenomenon,[55] it is difficult to separate the effects of sepsis, its complications, and adverse effects of the medications used in treatment from that of SAE in analysis of outcome data. A recent prospective study investigating cognitive impairment and functional disability among sepsis survivors found that severe sepsis was independently associated with a tripling in the odds of moderate-to-severe cognitive impairment.[58]

Critical Illness Polyneuropathy and Myopathy

As patients recover from the complexities of sepsis, new problems such as difficulty weaning from mechanical

ventilation or limb weakness may manifest. Critical illness polyneuropathy (CIP) is often preceded by SAE and represents a distal axonal sensorimotor polyneuropathy affecting limb and respiratory muscles; limb involvement is symmetrical and is most prominent in the lower extremities.[59] Diagnosis includes presence of all 4 criteria: critical illness with multiorgan failure and dysfunction; limb weakness or difficulty weaning patient from a ventilator after nonneuromuscular causes have been excluded; electrophysiological evidence of axonal motor and sensory polyneuropathy; and absence of a decremental response on repetitive nerve stimulation. Tendon reflexes may be normal in up to a third of patients, but loss of previously present reflexes can be an early sign.[60] Presence of CIP or critical illness myopathy (CIM) can be assessed during an evaluation of consciousness in a stuporous patient, as nail bed pressure will evoke weak to absent limb movements but obvious facial grimacing.[61]

It is important to identify the original illness responsible for the ICU admission as other conditions such as acidosis, prolonged effect of neuromuscular blockers in a patient with renal insufficiency, acute Guillain-Barré syndrome, decompensated myasthenia gravis, botulism, or acid maltase deficiency need to be considered.[60] Up to 80% of patients with severe sepsis develop CIP; those with mild forms may recover within weeks but slowing of nerve conduction has a poor prognosis.[60] The CIM frequently accompanies CIP and can be divided into 3 types: nonnecrotizing cachectic CIM, thick filament myopathy, and the acute necrotizing myopathy of critical care.[60] Glucocorticoids and proinflammatory cytokines are important mediators of muscular proteolysis, but diagnosis is established histopathologically as inflammatory changes are absent and creatinine kinase is often normal. Patients receiving high doses of corticosteroids alone or in combination with neuromuscular blocking agents may experience selective loss of myosin filaments that can progress to necrotizing myopathy with higher doses of neuromuscular blocking agents; in the latter instance, creatinine kinase is usually elevated.[60]

Notably, short duration of neuromuscular blockers and low-dose corticosteroids do not appear to increase the risk of muscle weakness. A study of 340 patients with severe ARDS defined as Pao_2/fraction of inspired oxygen (FIO_2) <150 who received 48 hours of either cisatracurium or placebo did not show a difference in the rate of ICU paresis between the groups.[62] A study of 128 patients with ARDS from the 25 hospitals examined factors contributing to ICU-acquired neuromyopathy and found that it was associated with prolonged mechanical ventilation, return to mechanical ventilation, and delayed return to home after critical illness, but treatment with methylprednisolone was not significantly linked with an increase in the risk of neuromyopathy.[63] A recent meta-analysis of low-dose methylprednisolone use in patients with ARDS showed an overall beneficial effect on mortality outcomes without increase in adverse events such as infection or neuromyopathy.[64] Lack of association of corticosteroid use and development of muscle weakness could likely be explained by the lower doses of steroids used in the more recent trials. Even though the above studies were performed on patients with ARDS, the extrapolation of these results on the patients with sepsis seems to be logical and justified, given many similarities and frequently noted comorbidity between sepsis and ARDS, both clinically and among research participants.

Sepsis in Patients With Neurological Diseases

Other Complications

Additional examples of neurological disorders that may manifest in patients with sepsis are Guillain-Barré syndrome following infective illness and muscle weakness due to severe associated electrolyte abnormalities.[65] Guillain-Barré syndrome is the most important differential diagnosis for CIP and is associated with an increase in mortality particularly in those requiring intubation.[66] Elevated cerebrospinal fluid protein and markedly slowed nerve conduction on EEG with prolonged or absent F waves and conduction block distinguish it from CIP as well as the presence of dysautonomia and abnormal blink reflex. Infections can also precipitate acute intermittent porphyria, with attacks including seizures, arrhythmia, abdominal pain, and psychiatric symptoms.[65]

Sepsis or trauma can result in acute rhabdomyolysis characterized by muscle pain and swelling, weakness, markedly elevated serum creatine kinase, and acute renal failure.[65] Sepsis can unmask a previously undiagnosed myasthenia gravis and is a common precipitant of a myasthenic crisis.[67] In addition to generalized weakness, patients manifest with ptosis and facial and bulbar weakness, and 85% to 90% are seropositive for acetylcholine receptor antibody; seronegative patients may have antibodies to muscle-specific tyrosine kinase. While sepsis has not been shown to play a role in the development of amyotrophic lateral sclerosis, individuals with this condition are more likely to be hospitalized for sepsis after diagnosis (hazard ratio: 2.6, 95% confidence interval: 1.9-3.5).[68]

Traumatic Brain Injury/Stroke

Traumatic brain injury (TBI) and stroke are associated with immune system suppression. Wolach et al investigated specific immune deficiencies in patients with TBI and found that neutrophil oxidative burst depressed 18 to 72 hours after the event. They also observed humoral deficiency in some patients, whereas the cellular arm was profoundly affected in most—circulating numbers of T cells, T helper cells, T suppressor cells, and natural killer cells were markedly reduced.[69] Moreover, any central nervous system (CNS) injury including stroke can lead to CNS-injury-induced immunodepression.[70] Experimental stroke has been shown to result in immunosuppression within hours of induction of ischemia via activation

of the hypothalamic–pituitary and sympathetic nervous systems, with focal cerebral ischemia leading to lymphocyte apoptosis and monocyte deactivation.[71] Up to 65% of patients with stroke develop infection, and bacterial pneumonia is the most common cause of death, not only via reduction in bulbar reflexes, increased drowsiness, dysphagia, and subsequent aspiration but also possibly via stroke-induced immune deficiency.[71] In a recent analysis of nonneurological sequelae in patients with severe TBI, sepsis was the most common complication and occurred in 75% of cases.[72] A study evaluating the risk of in-hospital death in 41 395 patients with TBI found that sepsis was independently associated with the risk of in-hospital death with a hazard ratio of 1.34 ($P < .001$) and that the severity of TBI was the strongest risk factor with a hazard ratio of 4.97 ($P < .001$).[73] Interestingly, administration of probiotics has been shown to attenuate the altered Th1/Th2 response induced by severe TBI.[74] But just as CNS-injury-induced immunosuppression can predispose to sepsis, severe sepsis itself can predispose patients to stroke via a new-onset atrial fibrillation.[75]

Prevention and Management Recommendations

The same general principles apply to prevention and management of sepsis in all patients, regardless of the involvement of primary or secondary organ system.

In regard to prevention, we would like to emphasize the following:

- Removal of central venous catheters as early as possible. While "safe" dwell times vary depending on the kind and site of the inserted catheter, it is prudent to reassess the needs for central venous catheters on daily basis and remove them promptly once the peripheral intravenous access seems clinically sufficient.
- Reduction in incidence of hospital-acquired infections with frequent hand washing/disinfection, barrier protections, 45° elevation of the head of the bed, oral antiseptic administration/hygiene at least twice daily, and early removal of Foley catheters.
- Early mobilization and ambulation.
- Encouraging the use of incentive spirometry.
- Maintaining adequate hydration and nutrition.
- Stress ulcer and deep venous thromboembolism prophylaxis.
- Keeping immunizations for both patients and health care staff up to date including influenza, streptococcal pneumonia, hepatitis, and meningitis vaccines, as appropriate.

In regard to management, we summarized the key elements of the sepsis management in context of the current literature and the "Surviving Sepsis Campaign":

- fluid resuscitation, early and goal-directed,
- appropriate cultures prior to antibiotic administration without delaying antibiotics,
- early targeted antibiotics and source control,
- use of vasopressors and/or inotropes after optimal fluid resuscitation, when needed,
- no empiric evaluation for adrenal insufficiency,consider stress doses of steroids in pressor-resistant shock and administer steroids to patients previously taking steroids in sufficient doses,
- target serum glucose at or below 150 mg/dL and limit the glycemic variability,
- protective lung ventilation strategy with low tidal volumes (6-8 mL/kg per ideal body weight) and low-to-moderate PEEP levels.
- narrow down antibiotic spectrum (deescalate) based on the results of culture and sensitivities, and/or clinical grounds, and
- facilitate early discontinuation of mechanical ventilation with daily awakening and spontaneous breathing trials.

Any patient in a hospital on any service can develop an infection, the initial manifestations of which may be subtle. Therefore, a high index of suspicion is required for prompt recognition of sepsis symptoms as early and aggressive management is needed to stop the progression of sepsis to septic shock and subsequent organ failure.

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